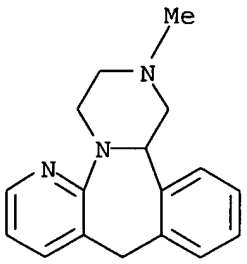
L1 ANSWER 3 OF 6 REGISTRY COPYRIGHT 2005 ACS on STN
RN 85650-52-8 REGISTRY
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl-, (±)-
OTHER NAMES:
CN 6-Azamianserin
CN Mepirzapin
CN Mepirzepine
CN **Mirtazapine**
CN Mirtazepine
CN Mirtazipine
CN Org 3770
CN Promyrtil
CN Remergil
CN Remergon
CN Remeron
CN Rexer
CN Zispin
FS 3D CONCORD
DR 61337-67-5, 82601-27-2
MF C17 H19 N3
CI COM
SR European Union (EU)
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, MSDS-OHS, PHAR, PIRA, PROMT, PROUSDDR, PS, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Book; Conference; Dissertation; Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: ANST (Analytical study); BIOL (Biological study); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study); PREP (Preparation)



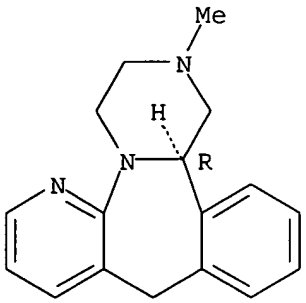
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

416 REFERENCES IN FILE CA (1907 TO DATE)
8 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
419 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 4 OF 6 REGISTRY COPYRIGHT 2005 ACS on STN
RN 61364-37-2 REGISTRY

CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl-, (14bR)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl-, (R)-
OTHER NAMES:
CN **(-)-Mirtazapine**
CN (R)-6-Azamianserin
CN (R)-Org 3770
CN Org 44-19
FS STEREOSEARCH
MF C17 H19 N3
CI COM
LC STN Files: ADISNEWS, BEILSTEIN*, BIOSIS, CA, CAPLUS, CHEMLIST, IFICDB, IFIPAT, IFIUDB, IMSPATENTS, IMSRESEARCH, PS, TOXCENTER
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Conference; Journal; Patent
RL.P Roles from patents: PREP (Preparation)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)

Absolute stereochemistry. Rotation (-).

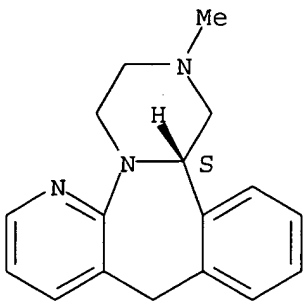


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

23 REFERENCES IN FILE CA (1907 TO DATE)
23 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 5 OF 6 REGISTRY COPYRIGHT 2005 ACS on STN
RN 61337-87-9 REGISTRY
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl-, (14bS)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl-, (S)-
OTHER NAMES:
CN **(+)-Mirtazapine**
CN (S)-6-Azamianserin
CN (S)-Org 3770
CN Org 44-20
FS STEREOSEARCH
MF C17 H19 N3
CI COM
LC STN Files: BEILSTEIN*, BIOSIS, CA, CAPLUS, CHEMLIST, IFICDB, IFIPAT, IFIUDB, IMSPATENTS, IMSRESEARCH, PS, TOXCENTER
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Conference; Journal; Patent
RL.P Roles from patents: PREP (Preparation)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)

Absolute stereochemistry. Rotation (+).



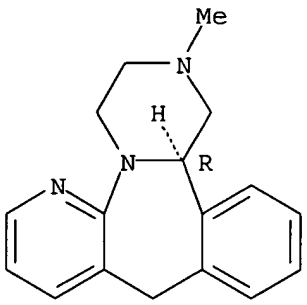
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

21 REFERENCES IN FILE CA (1907 TO DATE)
21 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=>

L1 ANSWER 4 OF 6 REGISTRY COPYRIGHT 2005 ACS on STN
RN 61364-37-2 REGISTRY
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl-, (14bR)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl-, (R)-
OTHER NAMES:
CN **(-)-Mirtazapine**
CN (R)-6-Azamianserin
CN (R)-Org 3770
CN Org 44-19
FS STEREOSEARCH
MF C17 H19 N3
CI COM
LC STN Files: ADISNEWS, BEILSTEIN*, BIOSIS, CA, CAPLUS, CHEMLIST, IFICDB, IFIPAT, IFIUDB, IMSPATENTS, IMSRESEARCH, PS, TOXCENTER
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Conference; Journal; Patent
RL.P Roles from patents: PREP (Preparation)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)

Absolute stereochemistry. Rotation (-).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

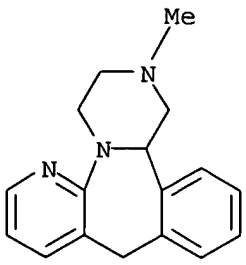
23 REFERENCES IN FILE CA (1907 TO DATE)
23 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:368674 CAPLUS
DOCUMENT NUMBER: 141:405919
TITLE: **Mirtazapine** is effective in the prophylactic treatment of chronic **tension**-type **headache**
AUTHOR(S): Bendtsen, Lars; Jensen, Rigmor
CORPORATE SOURCE: Danish Headache Center, University of Copenhagen, Copenhagen, Den.
SOURCE: Neurology (2004), 62(10), 1706-1711
CODEN: NEURAI; ISSN: 0028-3878
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background: The tricyclic antidepressant amitriptyline is the only drug with prophylactic efficacy for chronic **tension**-type **headache**. However, amitriptyline is only moderately effective, with **headache** reduction of approx. 30%, and treatment is often hampered by side effects. **Mirtazapine** is a relatively new so-called noradrenergic and specific serotonergic antidepressant, which is more specific and therefore generally better tolerated. Objective: To evaluate the efficacy of **mirtazapine**. Methods: Twenty-four non-depressed patients with chronic **tension**-type **headache** were included in a randomized, double-blind, placebo-controlled, crossover trial. All patients had tried numerous other treatments. **Mirtazapine** 15 to 30 mg/day or placebo was each given for 8 wk separated by a 2-wk wash-out period. Results: Twenty-two patients completed the study. The primary efficacy variable, area-under-the-**headache** curve (AUC; duration + intensity), was lower during treatment with **mirtazapine** (843) than during treatment with placebo (1,275) ($p = 0.01$). **Mirtazapine** also reduced the secondary efficacy variables **headache** frequency ($p = 0.005$), **headache** duration ($p = 0.03$), and **headache** intensity ($p = 0.03$) and was well tolerated. Conclusions: **Mirtazapine** reduced AUC by 34% more than placebo in difficult-to-treat patients. This finding is clin. relevant and may stimulate the development of prophylactic treatments with increased efficacy and fewer side effects for **tension**-type **headache** and other types of chronic pain.

IT **85650-52-8, Mirtazapine**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prophylactic treatment with **mirtazapine** in chronic **tension**-type **headache** patient is effective and well tolerated and reduced AUC, **headache** frequency, duration and intensity with fewer side effects)

RN 85650-52-8 CAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:140388 CAPLUS

L4 ANSWER 1 OF 4 MEDLINE on STN

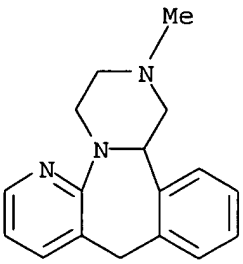
ACCESSION NUMBER: 2004580058 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15549531
TITLE: Therapy of primary headaches: the role of antidepressants.
AUTHOR: Colombo B; Annovazzi P O L; Comi G
CORPORATE SOURCE: Department of Neurology, Scientific Institute, Ospedale San Raffaele Headache Research Unit, Via Olgettina 48, Milan, Italy.. colombo.bruno@hsr.it
SOURCE: Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology, (2004 Oct) 25 Suppl 3 S171-5. Ref: 20
Journal code: 100959175. ISSN: 1590-1874.
PUB. COUNTRY: Italy
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200501
ENTRY DATE: Entered STN: 20041123
Last Updated on STN: 20050106
Entered Medline: 20050105

AB Antidepressants are included in evidence-based guidelines for the prophylactic therapy of migraine. Although they can cause several side effects depending on the neurochemical activity, and are to be used with caution in older patients, some of them have a well-documented efficacy. Amitriptyline is classified as a Group 1 drug, whereas Fluoxetine is included in Group 2. There is fair support for the effectiveness of other serotonine reuptake inhibitors in migraine prevention. Amitriptyline has demonstrated a consistent efficacy in Chronic **Tension** Type **Headache**, and **Mirtazapine** has a promising profile for the treatment of the same disease.

DOCUMENT NUMBER: 140:192924
TITLE: Pilot evaluation of **mirtazapine** for the treatment of hot flashes
AUTHOR(S): Perez, Domingo G.; Loprinzi, Charles L.; Barton, Debra L.; Pockaj, Barbara A.; Sloan, Jeff; Novotny, Paul J.; Christensen, Bradley J.
CORPORATE SOURCE: Mayo Clinic, Rochester, MN, 55905, USA
SOURCE: Journal of Supportive Oncology (2004), 2(1), 50-56
CODEN: JSOOBY; ISSN: 1544-6794
PUBLISHER: BioLink Communications, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This prospective, single-arm, pilot clin. trial, developed to evaluate the efficacy and tolerability of **mirtazapine** for alleviating hot flashes, was conducted between May 2001 and Jan. 2002. Patients' baseline characteristics were collected during the first week of the study. At the beginning of the second week, patients were started on **mirtazapine** at a dose of 7.5 mg at bedtime. The dose of **mirtazapine** was then increased to 15 mg at week 3 and to 30 mg at week 4. For week 5, patients could choose whether to take 15 mg/d or 30 mg/d. Data were obtained primarily from patient-completed questionnaires. Data from 22 evaluable women were available. For the 16 patients who completed the study, the median redns. in total daily hot flashes and weekly hot-flash scores from their baselines were 52.5% and 59.5%, resp. Patients reported improvements in **tension**, trouble sleeping, abnormal sweating, distress from hot flashes, satisfaction with hot-flash control, overall quality of life, and impact of hot flashes on quality of life. Patients also reported increases in appetite and dry mouth. Although data from a double-blind, placebo-controlled clin. trial would be necessary to more definitively elucidate the efficacy and toxicity of **mirtazapine** in patients with hot flashes, the available data suggest that **mirtazapine** is a reasonable treatment to consider in patients with hot flashes, particularly in those with anxiety and sleep disturbances.

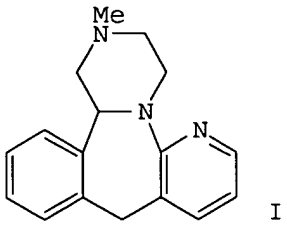
IT **85650-52-8, Mirtazapine**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**mirtazapine** for treatment of hot flashes)
RN 85650-52-8 CAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 78 THERE ARE 78 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

hypermotility of bilaterally olfactory-bulbectomized rats (a model of depression); only the largest dose of the drug reduced the motility of the sham-operated animals. The activity of this compound appears to reside in its S(+)isomer [**61337-87-9**]; the R(-)isomer [61364-37-2] being inactive. Bulbectomy was associated with a slight decrease in the concentration of noradrenaline [51-41-2] and its major metabolite MHPG [534-82-7] in the amygdaloid cortex and midbrain. Following chronic administration of (±)-Organic 3770, the concentration of noradrenaline and MHPG returned to control levels. When the enantiomers were tested, the behaviorally-inactive R(-)isomer was most effective in normalizing the deficit in this neurotransmitter. Thus, no correlation could be found between the behavioral activity of the enantiomers of Organic 3770 and changes in the metabolism of noradrenaline in the amygdaloid cortex and midbrain.

L2 ANSWER 2 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1982:608163 CAPLUS
DOCUMENT NUMBER: 97:208163
TITLE: Pharmaco-EEG study of 6-azamianserin (ORG 3770): dissociation of EEG and pharmacologic predictors of antidepressant activity
AUTHOR(S): Fink, Max; Irwin, Peter
CORPORATE SOURCE: Sch. Med., SUNY, Stony Brook, NY, USA
SOURCE: Psychopharmacology (Berlin, Germany) (1982), 78(1), 44-8
CODEN: PSCHDL; ISSN: 0033-3158
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

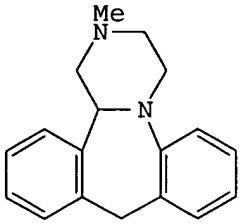


I

AB The effects of a single oral dose of 6-azamianserin (I) [61337-67-5] (2 mg) were compared to those of mianserin (6 mg), flurazepam (10 mg), and placebo in healthy male volunteers, in a crossover design. EEG and behavioral measures distinguished the substances from placebo. 6-Azamianserin was similar to mianserin in type and duration of effects. In a sep. study, 0.5 and 1.0 mg of the (+) [**61337-87-9**] and (-) [78684-63-6] enantiomers of 6-azamianserin elicited dose-related EEG and behavioral effects, distinguishable from placebo. These effects were similar to those elicited by racemic 6-azamianserin and mianserin. Clin. trials of 6-azamianserin in depressed patients, particularly the elderly and those with cardiovascular disease, are warranted. Dosages selected should be one-third those of mianserin. The stereospecific properties of the enantiomers in preclin. tests indicated that any clin. antidepressant activity will reside in the (+) isomer only, while the pharmaco-EEG trials suggested that both enantiomers will be clin. antidepressant. Clin. testing of the isomers, particularly the (-) isomer, is indicated as a test of the predictive value of pharmacol. and pharmaco-EEG models of clin. antidepressant activity.

L2 ANSWER 3 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1986:619415 CAPLUS
DOCUMENT NUMBER: 105:219415
TITLE: Antagonistic effects of some metabolites and analogs of mianserin on serotonin and α1- and α2-adrenergic receptors in the flexor reflex model in vivo
AUTHOR(S): Przegalinski, Edmund; Rawlow, Andrzej; Dohnal-Borak,

Iwona
CORPORATE SOURCE: Inst. Pharmacol., Pol. Acad. Sci., Krakow, 31-343, Pol.
SOURCE: Polish Journal of Pharmacology and Pharmacy (1986), 38(1), 69-75
CODEN: PJPPAA; ISSN: 0301-0244
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

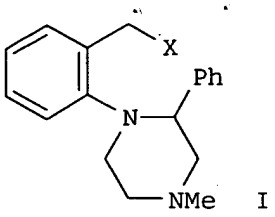
AB Mianserin (I) [24219-97-4], its 2 metabolites desmethylmianserin [71936-92-0] and 8-hydroxymianserin [57257-81-5], and its 2 analogs (R(-)-6-aza-mianserin [61364-37-2] and S(+)-6-aza-mianserin [**61337-87-9**] were tested for their antagonistic action on the central 5-HT receptor and α-adrenoceptors in the flexor reflex model in vivo in the spinal rat. The ability to reduce the increase in the flexor reflex activity induced by quipazine [4774-24-7] (a 5-HT receptor agonist), St 587 [15327-38-5] (an α1-adrenoceptor agonist), or clonidine [4205-90-7] (an α2-adrenocaptor agonist) was a measure of their potencies as antagonists of the resp. receptors. All the compds. occurred to be potent antagonists of the central 5-HT receptor (S(+)-6-aza-mianserin was most active) and, to a lesser degree, of α-adrenoceptors with preferential antagonistic action on α2-subtype.

L2 ANSWER 4 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:55224 CAPLUS
DOCUMENT NUMBER: 142:134623
TITLE: Preparation of enantiomerically pure (S)-mirtazapine
INVENTOR(S): Wieringa, Johannes Hubertus; Van De Ven, Adrianus Antonius Martinus; Kemperman, Gerardus Johannes
PATENT ASSIGNEE(S): Akzo Nobel N.V., Neth.
SOURCE: PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005005410	A1	20050120	WO 2004-EP51357	20040705

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: EP 2003-102095 A 20030710
GI



I

AB (S)-Mirtazapine was prepared using a ring closure reaction of (S)-pyridylpiperazine I (X = leaving group) using an acid and an organic solvent or in the absence of solvent. For example, (S)-1-(3-hydroxymethyl-2-pyridyl)-4-methyl-2-phenylpiperazine, I (X = OH), was dissolved in N-methylpyrrolidinone and polyphosphoric acid was added. The title compound was obtained in 68% yield with 99.2% ee.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 5 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:809207 CAPLUS

DOCUMENT NUMBER: 141:374383

TITLE: Enantioselective determination of the novel antidepressant mirtazapine and its active demethylated metabolite in human plasma by means of capillary electrophoresis

AUTHOR(S): Mandrioli, Roberto; Pucci, Vincenzo; Sabbioni, Cesare; Bartoletti, Claudio; Fanali, Salvatore; Raggi, Maria Augusta

CORPORATE SOURCE: Department of Pharmaceutical Sciences, Faculty of Pharmacy, Alma Mater Studiorum-University of Bologna, Bologna, 40126, Italy

SOURCE: Journal of Chromatography, A (2004), 1051(1-2), 253-260
CODEN: JCRAEY; ISSN: 0021-9673

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Mirtazapine is a recent noradrenergic and specific serotonergic antidepressant drug. A capillary electrophoretic method has been developed for the enantiosepn. and anal. of mirtazapine and its main active metabolite, N-desmethylmirtazapine, in human plasma. For method optimization several exptl. parameters were investigated, such as type and concentration of the chiral selector, buffer pH and capillary temperature Baseline enantiosepn. of the analytes was achieved in 2.5 min in a fused silica capillary (50 μm i.d.; 48.5 cm total length; 8.5 cm effective length) using carboxymethyl-β-cyclodextrin, dissolved in a background electrolyte consisting of 50 mM phosphate buffer at pH 2.5, as the chiral selector. UV detection was set at 205 nm. A careful pre-treatment of plasma samples was developed, using solid-phase extraction with hydrophilic-lipophilic balance cartridges (60 mg, 3 mL), eluting the sample with methanol, then concentrating it 37.5 times before injection. Extraction yield values are very satisfactory, being the average 89% for mirtazapine and 73% for N-desmethylmirtazapine. Application of the method to some human plasma samples has given satisfactory results.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 6 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:672566 CAPLUS

DOCUMENT NUMBER: 141:235556

TITLE: New method for the chiral evaluation of mirtazapine in human plasma by liquid chromatography

AUTHOR(S): Malagueno de Santana, Fernando Jose; Cesarino, Evandro Jose; Bonato, Pierina Sueli

CORPORATE SOURCE: Faculdade de Ciencias Farmaceuticas de Ribeirao Preto, Universidade de Sao Paulo, Ribeirao Preto, SP, CEP

14040-903, Brazil
SOURCE: Journal of Chromatography, B: Analytical Technologies in the Biomedical and Life Sciences (2004), 809(2), 351-356
CODEN: JCBAAI; ISSN: 1570-0232
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A simple, rapid and sensitive high-performance liquid chromatog. (HPLC) method was developed for the enantioselective anal. of the new antidepressant drug mirtazapine in human plasma. The procedure involved liquid-liquid extraction using toluene, followed by liquid chromatog. coupled to UV detection at 292 nm. The chromatog. separation of the (+)-(S)- and (-)-(R)-enantiomers of mirtazapine was achieved on a Chiralpak AD column (250 mm + 4.6 mm, 10 μm particle size) protected with a CN guard column, using hexane-ethanol (98:2, volume/volume) plus 0.1% diethylamine as the isocratic mobile phase, at a flow rate of 1.2 mL/min. The total anal. time was less than 12 min per sample. The recoveries of (+)-(S)- and (-)-(R)-mirtazapine were in the 88-111% range with a linear response over the 6.25-625 ng/mL concentration range for both enantiomers. The quantification limit (LOQ) was 5 ng/mL. Within-day and between-day assay precision and accuracy were studied at three concentration levels (10, 50 and 250 ng/mL). For both mirtazapine enantiomers, the coeffs. of variation (CV) and deviation from the theor. value were lower than 15% at all concentration levels. The method proved to be suitable for pharmacokinetic studies.
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 7 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:566070 CAPLUS
DOCUMENT NUMBER: 142:147742
TITLE: Chirality in the New Generation of Antidepressants: Stereoselective Analysis of the Enantiomers of Mirtazapine, N-Demethylmirtazapine, and 8-Hydroxymirtazapine by LC-MS
AUTHOR(S): Paus, Erik; Jonzier-Perey, Michele; Cochard, Nathalie; Eap, Chin B.; Baumann, Pierre
CORPORATE SOURCE: Unite de Biochimie et Psychopharmacologie Clinique, University Department of Adult Psychiatry, Prilly-Lausanne, CH-1008, Switz.
SOURCE: Therapeutic Drug Monitoring (2004), 26(4), 366-374
CODEN: TDMODV; ISSN: 0163-4356
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mirtazapine is an antidepressant that acts specifically on noradrenergic and sertonergic receptors. A LC-MS method was developed that allows the simultaneous anal. of the R-(-)- and S-(+)-enantiomers of mirtazapine (MIR), demethylmirtazapine (DMIR), and 8-hydroxymirtazapine (8-OH-MIR) in plasma of MIR-treated patients. The method involves a 3-step liquid-liquid extraction, an HPLC separation on a Chirobiotic V column, and MS detection in electrospray mode. The limit of quantification (LOQ) for all enantiomers was 0.5 ng/mL, and the intra- and interday CVs were within 3.3% to 11.7% (concentration ranges 5-50 ng/mL). A method is also presented for the quant. anal. of glucuroconjugated MIR and 8-OH-MIR. S-(+)-8-OH-MIR is present in plasma mainly as its glucuronide. Preliminary data suggest that in all patients, except in those comedicated with CYP2D6 inhibitors such as fluoxetine and thioridazine, R-(-)-MIR concns. were higher than those of S-(+)MIR. Moreover, fluvoxamine seems also to inhibit the metabolism of MIR. Therefore, this method seems to be suitable for the stereoselective assay of MIR and its metabolites in plasma of patients comedicated with MIR and other drugs for routine and research purposes.
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 8 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:818797 CAPLUS
DOCUMENT NUMBER: 138:395329

TITLE: Biotransformation of mirtazapine by Cunninghamella elegans
AUTHOR(S): Moody, Joanna D.; Freeman, James P.; Fu, Peter P.; Cerniglia, Carl E.
CORPORATE SOURCE: Division of Microbiology, National Center for Toxicological Research, Jefferson, AR, 72079, USA
SOURCE: Drug Metabolism and Disposition (2002), 30(11), 1274-1279
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The fungus Cunninghamella elegans was used as a microbial model of mammalian metabolism to biotransform the tetracyclic antidepressant drug mirtazapine, which is manufactured as a racemic mixture of R(-)- and S(+)-enantiomers. In 168 h, C. elegans transformed 91% of the drug into the following seven metabolites: 8-hydroxymirtazapine, N-desmethyl-8-hydroxymirtazapine, N-desmethylmirtazapine, 13-hydroxymirtazapine, mirtazapine N-oxide, 12-hydroxymirtazapine, and N-desmethyl-13-hydroxymirtazapine. CD spectral anal. of unused mirtazapine indicated that it was slightly enriched with the R(-)-enantiomer. When the fungus was treated with the optically pure forms of the drug, the S(+)-enantiomer produced all seven metabolites whereas the R(-)-enantiomer produced only 8-hydroxymirtazapine, N-desmethyl-8-hydroxymirtazapine, N-desmethylmirtazapine, and mirtazapine N-oxide. C. elegans produced five mammalian and two novel metabolites and is therefore a suitable microbial model for mirtazapine metabolism
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 9 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:871440 CAPLUS
DOCUMENT NUMBER: 137:72526
TITLE: In vitro metabolism of mirtazapine enantiomers by human cytochrome P450 enzymes
AUTHOR(S): Dodd, Seetal; Boulton, David W.; Burrows, Graham D.; DeVane, C. Lindsay; Norman, Trevor R.
CORPORATE SOURCE: Department of Psychiatry, Austin and Repatriation Medical Centre, University of Melbourne, Heidelberg, 3084, Australia
SOURCE: Human Psychopharmacology (2001), 16(7), 541-544
CODEN: HUPSEC; ISSN: 0885-6222
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The metabolism of mirtazapine enantiomers was investigated in vitro using human lymphoblast microsomes transfected with human cDNA to over-express either CYP1A2, CYP2C9, CYP2C19, CYP2D6 or CYP3A4 and assayed for mirtazapine enantiomers using a validated chiral method of high-performance liquid chromatog. (+)-Mirtazapine was extensively metabolized by CYP2D6 (Km=9.3±3.3 μmol/L, Vmax=40.9±7.9 μmol/h/mg, intrinsic clearance=4.41 L/h/mg). CYP1A2 and CYP3A4 showed low metabolic activity toward (+)-mirtazapine and (-)-mirtazapine, resp. Neither CYP2C9 nor CYP2C19 appeared to be involved in the metabolism of the enantiomers of mirtazapine.
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 10 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:816071 CAPLUS
DOCUMENT NUMBER: 134:65754
TITLE: Chiral determination of mirtazapine in human blood plasma by high-performance liquid chromatography
AUTHOR(S): Dodd, Seetal; Burrows, Graham D.; Norman, Trevor R.
CORPORATE SOURCE: Department of Psychiatry, Austin & Repatriation Medical Centre, University of Melbourne, Heidelberg, 3084, Australia

SOURCE: Journal of Chromatography, B: Biomedical Sciences and Applications (2000), 748(2), 439-443
CODEN: JCBBEP; ISSN: 0378-4347
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A method is described for the determination of the two enantiomers of mirtazapine in human blood plasma by HPLC. Measurements were performed on drug free plasma spiked with mirtazapine and used to prepare and validate standard curves. Levels of enantiomers of mirtazapine were also measured in patients being treated for depression with racemic mirtazapine. Mirtazapine was separated from plasma by solid-phase extraction using CERTIFY columns. Chromatog. separation was achieved using a Chiralpak AD column and pre-column and compds. were detected by their absorption at 290 nm. Imipramine was used as an internal standard The assay was validated for each analyte in the concentration range 10-100 ng/mL. The coefficient of variance was 16% and 5.5% for (+)-mirtazapine for 10 and 100 ng/mL control specimens resp. and 15% and 7.3% for mirtazapine for 10 and 100 ng/mL control specimens resp. This assay is appropriate for use in the clin. range. The range of plasma mirtazapine concns. from eleven patients taking daily doses of 30-45 mg of racemate was <5 to 69 ng/mL for (+)-mirtazapine and 13-88 ng/mL for (-)-mirtazapine for blood specimens collected 10-17.5 h after taking the dose.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 11 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:611266 CAPLUS
DOCUMENT NUMBER: 130:415
TITLE: Neurochemical effects of the enantiomers of mirtazapine in normal rats
AUTHOR(S): McGrath, Caroline; Burrows, Graham D.; Norman, Trevor R.
CORPORATE SOURCE: Department of Psychiatry, Austin and Repatriation Medical Centre, Heidelberg, 3084, Australia
SOURCE: European Journal of Pharmacology (1998), 356(2/3), 121-126
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The present study was designed to examine the neurochem. effects of (±)-mirtazapine (10 mg kg-1 i.p.) and its enantiomers in rats. Male Sprague-Dawley rats received either (+)-mirtazapine, (-)-mirtazapine, (±)-mirtazapine or vehicle, by i.p. injection for two weeks. Maximum change in temperature from baseline, following a single dose of the 5-HT1A receptor agonist 8-Hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) (0.15 mg kg-1 s.c.), was used to assess the function of the 5-HT1A receptors. Chronic drug treatment potentiated this response, with (±)-mirtazapine>(-)-mirtazapine>(+)-mirtazapine. Receptor changes were also observed with a slight decrease in β1-adrenoceptor d., although this failed to reach significance. A significant decrease in β1-adrenoceptor affinity was observed following (-)-mirtazapine treatment. All drugs tested significantly reduced the d. of the 5-HT2 receptors. Results of the present study suggest that in so far as alterations in these receptor populations are important for the therapeutic action of antidepressants, neither of the enantiomers appear to be more active than the racemic mixture

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 12 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:267897 CAPLUS
DOCUMENT NUMBER: 129:8662
TITLE: Direct enantiomeric separation of mianserin and 6-azamianserin derivatives using chiral stationary phases
AUTHOR(S): Selditz, Ulrike; Liao, Yi; Franke, Jan Piet; de Zeeuw,

Rokus A.; Wikstrom, Hakan
CORPORATE SOURCE: Department of Analytical Chemistry and Toxicology, GIDS (Groningen Institute for Drug Studies), University Centre for Pharmacy, Antonius Deusinglaan 1, Groningen, 9713 AV, Neth.
SOURCE: Journal of Chromatography, A (1998), 803(1 + 2), 169-177
CODEN: JCRAEY; ISSN: 0021-9673
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The direct enantiomeric separation of mianserin and 6-azamianserin and some of their derivs. by HPLC using two different chiral selectors was investigated. Mobile phases of n-hexane/ethanol (95:5) or n-hexane/isopropanol (90:10) with added 0.1% triethylamine were used. For the cellulose-based Chiralcel OD column, a strong relation between the lipophilicity of the compds. and the retention behavior was observed To some extent, this was also found for the enantiomeric separation on the amylose-based Chiralpak AD column. In some cases a complementary behavior of these two phases was observed; racemic mixts. that could not be separated by one column could be resolved by the other column.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 13 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:146086 CAPLUS
DOCUMENT NUMBER: 128:238932
TITLE: Pharmacokinetics and biotransformation of mirtazapine in human volunteers
AUTHOR(S): Delbressine, L. P. C.; Moonen, M. E. G.; Kaspersen, F. M.; Wagenaars, G. N.; Jacobs, P. L.; Timmer, C. J.; Paanakker, J. E.; Van Hal, H. J. M.; Voortman, G.
CORPORATE SOURCE: Department of Drug Metabolism and Kinetics, N.V. Organon, Oss, Neth.
SOURCE: Clinical Drug Investigation (1998), 15(1), 45-55
CODEN: CDINFR; ISSN: 1173-2563
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This paper investigated the pharmacokinetics and biotransformation of mirtazapine in healthy human volunteers. The results showed that the area under the plasma drug concentration-time curve (AUC) of mirtazapine in human plasma appeared to be three times higher than the AUC of demethylmirtazapine. As mirtazapine is marketed as a racemic mixture and both enantiomers possess pharmacol. properties essential for the overall activity of the racemate, the pharmacokinetics of mirtazapine were examined and appeared to be enantioselective. The R(-)-enantiomer showed the longest elimination half-life from plasma. This was ascribed to the preferred formation of a quaternary ammonium glucuronide of the R(-)-enantiomer. This glucuronide may be deconjugated, leading to a further circulation of the parent compound, thus causing a prolongation in the elimination half-life. The S(+)-enantiomer was preferentially metabolized into an 8-hydroxy glucuronide. Other metabolic transformation pathways found for mirtazapine were demethylation and N-oxidation Mirtazapine was extensively metabolized and almost completely excreted in the urine (over 80%) and feces within a few days after oral administration.
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 14 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:808034 CAPLUS
DOCUMENT NUMBER: 128:149531
TITLE: Pharmacological profile of antidepressants and related compounds at human monoamine transporters
AUTHOR(S): Tatsumi, Masahiko; Groshan, Karen; Blakely, Randy D.; Richelson, Elliott
CORPORATE SOURCE: San Pablo Road, Mayo Clinic Jacksonville,

Jacksonville, FL 32224, 4500, USA
SOURCE: European Journal of Pharmacology (1997), 340(2/3), 249-258
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Using radioligand binding assays, we determined the equilibrium dissociation consts. (KD's) for 37 antidepressants, three of their metabolites (desmethylcitalopram, desmethylsertraline, and norfluoxetine), some mood stabilizers, and assorted other compds. (some antiepileptics, Ca2+ channel antagonists, benzodiazepines, psychostimulants, antihistamines, and monoamines) for the human serotonin, norepinephrine, and dopamine transporters. Among the compds. that we tested, mazindol was the most potent at the human norepinephrine and dopamine transporters with KD's of 0.45±0.03 nM and 8.1±0.4 nM, resp. Sertraline (KD=25±2 nM) and nomifensine (56±3 nM) were the two most potent antidepressants at the human dopamine transporter. We showed significant correlations for antidepressant affinities at binding to serotonin (R=0.93), norepinephrine (R=0.97), and dopamine (R=0.87) transporters in comparison to their resp. values for inhibiting uptake of monoamines into rat brain synaptosomes. These data are useful in predicting some possible adverse effects and drug-drug interactions of antidepressants and related compds.
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

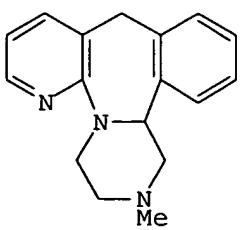
L2 ANSWER 15 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:911437 CAPLUS
DOCUMENT NUMBER: 124:44651
TITLE: Pharmacokinetics and metabolism studies with 13C-labeled mirtazapine
AUTHOR(S): Sperling, Eric; Delbressine, Leon; van Hal, Henk; Kaspersen, Frans
CORPORATE SOURCE: N. V. Organon, Oss, 5340 BH, Neth.
SOURCE: Synthesis and Applications of Isotopically Labelled Compounds 1994, Proceedings of the International Symposium, 5th, Strasbourg, June 20-24, 1994 (1995), Meeting Date 1994, 827-30. Editor(s): Allen, John; Voges, Rolf. Wiley: Chichester, UK.
CODEN: 61UMAF
DOCUMENT TYPE: Conference
LANGUAGE: English
AB The pharmacokinetics and metabolism of mirtazapine and its enantiomers is described 13C-labeled mirtazapine and the 13C-labeled pseudoracemate.

L2 ANSWER 16 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:426255 CAPLUS
DOCUMENT NUMBER: 121:26255
TITLE: Interaction between enantiomers of mianserin and ORG3770 at 5-HT3 receptors in cultured mouse neuroblastoma cells
AUTHOR(S): Kooyman, A. R.; Zwart, R.; Vanderheijden, P. M. L.; van Hooft, J. A.; Vijverberg, H. P. M.
CORPORATE SOURCE: Res. Inst. Toxicol., Utrecht Univ., Utrecht, NL-3508, Neth.
SOURCE: Neuropharmacology (1994), 33(3-4), 501-7
CODEN: NEPHBW; ISSN: 0028-3908
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Stereoselective effects of mianserin and ORG3370 on serotonin 5-HT3 receptors in mouse neuroblastoma N1E-115 cells have been investigated in radioligand binding and in whole-cell voltage clamp expts. The specific binding of [3H]GR65630 to 5-HT3 recognition sites in N1E-115 cell homogenates is reduced by mianserin and ORG3770 and their enantiomers. The pKi values of the more potent (R)-enantiomers of mianserin and ORG3770 are 15 and 37 times more potent than their resp. (S)-enantiomers. The racemates are only 1.9 and 3.3 times less potent than the corresponding (R)-enantiomers. In voltage clamp expts. the (R)-enantiomers block the

5-hydroxytryptamine (5-HT)-induced ion current with pIC50 values of 8.52 for (R)-mianserin and 8.26 for the (R)-enantiomer of ORG3770. The (R)-enantiomers of mianserin and ORG3770 are 24 and 145 times more potent in blocking the 5-HT-induced ion current than their resp. (S)-enantiomers. The racemates are 6 and 13 times less than the corresponding (R)-enantiomers. In addition, the block of 5-HT-induced ion current by the (R)-enantiomer of ORG3770 is partially reversed by a low concentration of its (S)-enantiomer. The results indicate that the two enantiomers block the 5-HT3 receptor-mediated ion current in a mutually dependent manner.

L2 ANSWER 17 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:28250 CAPLUS
DOCUMENT NUMBER: 116:28250
TITLE: Applicability of new chiral stationary phases in the separation of racemic pharmaceutical compounds by high-performance liquid chromatography
AUTHOR(S): Maris, F. A.; Vervoort, R. J. M.; Hindriks, H.
CORPORATE SOURCE: Pharma Div., AKZO, Oss, 5340 BH, Neth.
SOURCE: Journal of Chromatography (1991), 547(1-2), 45-58
CODEN: JOCRAM; ISSN: 0021-9673
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The potential of contemporary chiral liquid chromatog. columns for the enantiosepn. of racemates of pharmaceutical compds. was studied. Sixteen Organon compds. were selected, mostly cardiovascular or CNA-active drugs. Seven chiral stationary phases were used, viz., five different cellulose derivs., an α1-acid glycoprotein and a polymethacylate phase, all coated on silica particles. A good enantiosepn., with a resolution higher than 1.0, was achieved for fifteen of the sixteen racemates. The best results were obtained on a Chiralcel OJ column, on which seven enantiomers were separated With respect to the chromatog. performance, stability and/or selectivity, the cellulose derivs. (Chiralcel columns) were preferred over the protein and polymethacrylate columns.

L2 ANSWER 18 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1988:447845 CAPLUS
DOCUMENT NUMBER: 109:47845
TITLE: Neurochemical and autonomic pharmacological profiles of the 6-aza-analog of mianserin, Org 3770 and its enantiomers
AUTHOR(S): De Boer, T.; Maura, G.; Raiteri, M.; De Vos, C. J.; Wieringa, J.; Pinder, R. M.
CORPORATE SOURCE: Dep. CNS Pharmacol., Organon Int. B.V., OSS, 5340 BH, Neth.
SOURCE: Neuropharmacology (1988), 27(4), 399-408
CODEN: NEPHBW; ISSN: 0028-3908
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

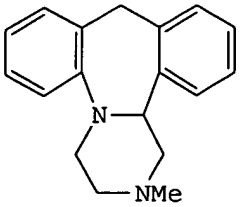
AB The neurochem. and autonomic pharmacol. profile of 1,2,3,4,10,14b-hexahydro-2-methylpyrazino[2,1-a]pyrido[2,3-c][2]benzazepine (I; (±)Org 3770) and the related antidepressant drug, mianserin, were compared. The uptake of [3H]noradrenaline ([3H]NA) in vitro was weakly affected by (±)Org 3770 (pKi = 5.6) in contrast to mianserin (pKi = 7.4). Both (±)Org 3770 and mianserin facilitated the release of [3H]NA in slices

of cortex. The effects of NA mediated by α2-adrenoceptors on the release of both [3H]NA or [3H]serotonin ([3H]5-HT) were antagonized by (+)Org 3770 with pKi values of 8.4 and 8.1, resp. However, (-)Org 3770 only antagonized the effects of NA on the release of [3H]5-HT (pA2 = 7.7). The binding of [3H]rauwolscine to α2-adrenoceptors was inhibited by (±)Org 3770 and mianserin with identical affinity (pKi = 7.0), whereas the binding of [3H]prazosin to α1-adrenoceptors was less potently affected by (±)Org 3770 (pK2 = 6.4) than by mianserin (pKi = 7.1). A similar difference was found for α1- and α2-adrenoceptors in vas deferens of the rat. The binding of [3H]mianserin to 5-HT2 receptors was less potently blocked by (±)Org 3770 (pKi = 8.1) than by mianserin (pKi = 9.4) while the binding of [3H]mepyramine to histamine-1 receptors was more potently affected by (±)Org 3770 (pKi = 9.3) than by mianserin (pKi = 8.75). The binding of [3H]quinuclidinylbenzilate to muscarinic cholinergic receptors was blocked equally by (+)Org 3770 (pKi = 6.1) and mianserin (pKi = 6.3). Similar data on tryptamine-D, histamine-1 and muscarinic cholinergic receptors in isolated organs were obtained. A prominent role for the blockade of α2-adrenoceptors in the therapeutic effects of mianserin and (+)Org 3770 in depression is suggested, probably excluding a role of inhibition of the uptake of NA.

L2 ANSWER 19 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1988:198225 CAPLUS
DOCUMENT NUMBER: 108:198225
TITLE: Pharmacological evaluation of in vivo tests for α2-adrenoceptor blockade in the central nervous system and the effects of the enantiomers of mianserin and its aza-analog ORG 3770
AUTHOR(S): Gower, A. J.; Broekkamp, C. L. E.; Rijk, H. W.; Van Delft, A. M. L.
CORPORATE SOURCE: Dep. CNS-Pharmacol., Organon Int. BV, Oss, Nl-5340 BH, Neth.
SOURCE: Archives Internationales de Pharmacodynamie et de Therapie (1988), 291, 185-201
CODEN: AIPTAK; ISSN: 0003-9780
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A series of compds. with actions on the central nervous system was tested for antagonism of clonidine-induced sleep in chicks and clonidine-induced mydriasis in rats for the purpose of evaluating these methods as tests for demonstrating an in vivo α2-adrenoceptor blocking effect of a novel compound Clonidine-induced mydriasis was the most selective method. The order of potency for compds. fully antagonizing clonidine-induced mydriasis was MSD 26 > piperoxan > yohimibine > mianserin > tolazoline. Partial antagonism was found for quipazine and sulpiride. Misleading results can arise from the involvement of cholinergic mechanisms in the control of the pupil diameter The order of potency for compds. antagonizing clonidine-induced sleep in chicks was apomorphine > yohimbine > idazoxan > aptazapine = MSD 26 > quipazine > methysergide > piperoxan = mianserin : bepridil = metergoline = cyproheptadine = desipramine > tolazoline > dexchlorpheniramine, although antagonism was not complete for all of these compds. Misleading results can arise from effects on arousal of the chicks but cholinergic mechanisms do not play a disturbing role so that the method with chicks can be a useful supplement to the mydriasis method. The enantiomers of mianserin and of a compound related to mianserin, Org 3770, were tested in the 2 methods; the α2-blocking effect of these compds. resided in the S(+)-enantiomers.

L2 ANSWER 20 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1982:400292 CAPLUS
DOCUMENT NUMBER: 97:292
TITLE: Presynaptic α-block and inhibition of noradrenaline and 5-hydroxytryptamine reuptake by a series of compounds related to mianserin
AUTHOR(S): Nickolson, Victor J.; Wieringa, Joop H.
CORPORATE SOURCE: Org. Sci. Dev. Group, Oss, Neth.
SOURCE: Journal of Pharmacy and Pharmacology (1981), 33(12), 760-6

CODEN: JPPMAB; ISSN: 0022-3573
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB A structure-activity relationship study was undertaken for a variety of structural analogs of the tetracyclic antidepressant mianserin (I) [24219-97-4]. Presynaptic α-blocking activity in vitro was evaluated measuring the potentiation of depolarization-induced noradrenaline (II) [51-41-2] release from rat cerebral cortex slices. Inhibition of II and 5HT [50-67-9] reuptake was measured in rat hypothalamic or striatal synaptosomes, resp. Presynaptic α-blockade was only found in mols. with an overall bent shape. Flat rigid mols. or flexible ones were not active. Six-membered, chair-formed D-rings (containing the -NMe moiety) appeared better than 5- or 7-membered ones. Heteroatom substitution, but not hydroxylation or methylation, of the bridge between the two aromatic rings left presynaptic α-blockade unaffected. N-demethylation and aromatic Me- or Cl-substitution reduced presynaptic α-blockade. In pyridine ring-substituted analogs, the localization of the heteroatom appeared to be crucial. Reuptake inhibitor activity was only found in desmethylmianserin [71936-92-0]. II reuptake inhibition was found in many I analogs, especially those with an exocyclic -N(Me)2 moiety. Structure-activity relationships for II reuptake inhibition differed from those for presynaptic α-blockade and were generally less stringent. For both properties, simple additivity relationships appeared to be absent.

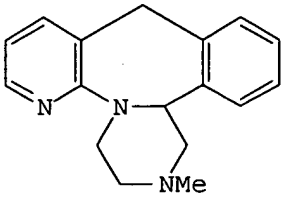
L2 ANSWER 21 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1977:29883 CAPLUS
DOCUMENT NUMBER: 86:29883
TITLE: Heterocyclic tetracyclic compounds
INVENTOR(S): Van der Burg, Willem J.
PATENT ASSIGNEE(S): AKZO N. V., Neth.
SOURCE: Ger. Offen., 40 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 2614406	A1	19761014	DE 1976-2614406	19760402
DE 2614406	C2	19920220		
NL 7504075	A	19761007	NL 1975-4075	19750405
NL 189199	B	19920901		
NL 189199	C	19930201		
ZA 7601756	A	19770330	ZA 1976-1756	19760323
AU 7612361	A1	19770929	AU 1976-12361	19760325
GB 1543171	A	19790328	GB 1976-12270	19760326
CH 622261	A	19810331	CH 1976-3886	19760329
DK 7601426	A	19761006	DK 1976-1426	19760330
DK 142498	B	19801110		
DK 142498	C	19810706		
FI 62087	B	19820730	FI 1976-884	19760401
FI 62087	C	19821110		
BE 840362	A1	19761004	BE 1976-165832	19760402

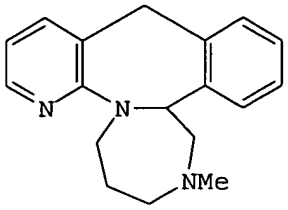
SE 7603931	A	19761006	SE 1976-3931	19760402
SE 422941	B	19820405		
SE 422941	C	19820715		
JP 51122099	A2	19761025	JP 1976-37678	19760402
JP 59042678	B4	19841016		
FR 2305986	A1	19761029	FR 1976-9686	19760402
FR 2305986	B1	19800613		
ES 446634	A1	19771101	ES 1976-446634	19760402
CA 1076571	A1	19800429	CA 1976-249439	19760402
HU 21859	O	19820227	HU 1976-AO437	19760405
HU 179401	B	19821028		

PRIORITY APPLN. INFO.: NL 1975-75040 A 19750405
NL 1975-4075 19750405

GI



I



II

AB The title compds., e.g. I and II, with nervous system-depressant and antihistaminic activities (no data), are prepared by various procedures. Thus, reaction of 2-chloronicotinonitrile with 1-methyl-3-phenylpiperazine gives 2-(4-methyl-2-phenyl-1-piperazinyl)-3-pyridinecarbonitrile which is hydrolyzed to the carboxylic acid which is reduced to the hydroxymethyl derivative (III). Cyclization of 3.25 g III in concentrated H2SO4 at 20-35° gives after 2 hr and treatment with NH4OH 2.43 g I.

```
Connecting via Winsock to STN



Welcome to STN International!  Enter x:x

LOGINID:SSSPTA1616BSK

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2


* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1           Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2           "Ask CAS" for self-help around the clock
 NEWS  3  SEP 01   New pricing for the Save Answers for SciFinder Wizard within
                   STN Express with Discover!
 NEWS  4  OCT 28   KOREAPAT now available on STN
 NEWS  5  NOV 30   PHAR reloaded with additional data
 NEWS  6  DEC 01   LISA now available on STN
 NEWS  7  DEC 09   12 databases to be removed from STN on December 31, 2004
 NEWS  8  DEC 15   MEDLINE update schedule for December 2004
 NEWS  9  DEC 17   ELCOM reloaded; updating to resume; current-awareness
                   alerts (SDIs) affected
 NEWS  10 DEC 17   COMPUAB reloaded; updating to resume; current-awareness
                   alerts (SDIs) affected
 NEWS  11 DEC 17   SOLIDSTATE reloaded; updating to resume; current-awareness
                   alerts (SDIs) affected
 NEWS  12 DEC 17   CERAB reloaded; updating to resume; current-awareness
                   alerts (SDIs) affected
 NEWS  13 DEC 17   THREE NEW FIELDS ADDED TO IFIPAT/IFIUDB/IFICDB
 NEWS  14 DEC 30   EPFULL: New patent full text database to be available on STN
 NEWS  15 DEC 30   CAPLUS - PATENT COVERAGE EXPANDED
 NEWS  16 JAN 03   No connect-hour charges in EPFULL during January and
                   February 2005
 NEWS  17 JAN 26   CA/CAPLUS - Expanded patent coverage to include the Russian
                   Agency for Patents and Trademarks (ROSPATENT)
 NEWS  18 FEB 10   STN Patent Forums to be held in March 2005
 NEWS  19 FEB 16   STN User Update to be held in conjunction with the 229th ACS
                   National Meeting on March 13, 2005

 NEWS EXPRESS  JANUARY 10 CURRENT WINDOWS VERSION IS V7.01a, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 10 JANUARY 2005

 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS INTER    General Internet Information
 NEWS LOGIN    Welcome Banner and News Items
 NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
 NEWS WWW      CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that
specific topic.

  All use of STN is subject to the provisions of the STN Customer
  agreement.  Please note that this agreement limits use to scientific
  research.  Use for software development or design or implementation
  of commercial gateways or other similar uses is prohibited and may
  result in loss of user privileges and other penalties.

  * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 20:25:24 ON 18 FEB 2005

=> file caplus
```

COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'CAPLUS' ENTERED AT 20:25:38 ON 18 FEB 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 18 Feb 2005 VOL 142 ISS 9
FILE LAST UPDATED: 17 Feb 2005 (20050217/ED)

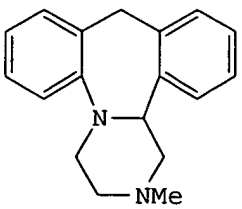
This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> s 61337-87-9/rn
            21 61337-87-9
             0 61337-87-9D
L1           21 61337-87-9/RN
                (61337-87-9 (NOTL) 61337-87-9D )

=> focus
PROCESSING COMPLETED FOR L1
L2            21 FOCUS L1 1-

=> d ibib abs 1-21
```

L2 ANSWER 1 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1986:400478 CAPLUS
DOCUMENT NUMBER: 105:478
TITLE: Effect of chronic administration of the 6-aza analog of mianserin (Organic 3770) and its enantiomers on behavior and changes in noradrenaline metabolism of olfactory-bulbectomized rats in the "open field" apparatus
AUTHOR(S): O'Connor, W. T.; Leonard, B. E.
CORPORATE SOURCE: Dep. Pharmacol., Univ. Coll., Galway, Ire.
SOURCE: Neuropharmacology (1986), 25(3), 267-70
CODEN: NEPHBW; ISSN: 0028-3908
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB Following its chronic administration, the racemic mianserin analog (±)-Org 3770 (I) [**61337-87-9**] (0.5-2.0 mg/kg) attenuated the